UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/574,129	11/02/2006	Chuan-Yuan Li	180/179 PCT/US	9249

25297 7590 10/16/2009

JENKINS, WILSON, TAYLOR & HUNT, P. A.
Suite 1200 UNIVERSITY TOWER
3100 TOWER BLVD.,
DURHAM, NC 27707

EXAMINER	
BOWMAN, AMY HUDSON	
ART UNIT	PAPER NUMBER
1635	
MAIL DATE	DELIVERY MODE
10/16/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/574,129	LI ET AL.	
	Examiner	Art Unit	
	AMY BOWMAN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 June 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36,38-42,45-59 and 62-65* is/are pending in the application.

4a) Of the above claim(s) *1-35,64 and 65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36, 38-42, 45-59, 62, and 63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 March 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed 6/18/09 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 12/18/08 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-36, 38-42, 45-59, and 62-65 are pending in the instant application.

Applicant's arguments regarding the sequences of claims 64 and 65 have been considered but are not persuasive because the sequences do not in fact comprise instant SEQ ID NO: 7, but are rather off by a nucleotide (comprise a preceding "g" rather than the last "t" of instant SEQ ID NO: 7). Should the sequences be shifted to in fact comprise SEQ ID NO: 7, they would be included in the rejection under 35 USC 103(a) below because Reich et al. teaches the addition of nucleotide linker sequences.

This application contains claims 1-35, 64, and 65, that are drawn to an invention nonelected with traverse in the reply filed on 1/4/08. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicant's amendments and/or arguments filed 6/18/09 have been fully considered and are persuasive. Therefore, the rejections have been withdrawn.

However, in view of the instant claim amendments, which have altered the priority date of the instant claims, new grounds of rejection are applied.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/508,145, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The provisional application does not teach a siRNA sequence wherein the sense region is identical to instant SEQ ID NO: 7. Upon a review of the provisional document, the closest sequence appears to be SEQ ID NO: 7 of the provisional application, which is not identical to instant SEQ ID NO: 7.

Furthermore, claim 36 has been amended to require for the sense region to be between 19 and 30 base pairs in length with no length limitation for the antisense region. It is noted that the sense region would not be 19 to 30 "base pairs" in length, but rather 19 to 30 bases in length given that the sense region is within one strand. Appropriate correction/explanation is required.

Furthermore, the instant specification does not disclose or contemplate siRNA molecules wherein the sense region is 19 to 30 nucleotides in length and the antisense region has no length limit, thereby embracing those with much longer antisense regions.

None of the priority documents disclose support for this limitation in the context of the instant claims. Should applicants disagree, applicants are encouraged to point with particularity by page and line number to where such support exists.

Therefore, the instant claims are accorded an effective filing date of 11/2/06, the filing date of the instant application.

It is noted that the rejection under 35 USC 103(a) as set forth below is necessitated by the instant claim amendment, which has established a new priority date.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 36, 38-42, 45-59, 62, and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reich et al. (US 7,521,431 B2), in view of Fosnaugh et al. (US 2003/0143732 A1).

The instant claims are directed to a small interfering RNA (siRNA) molecule that down regulates expression of a human hypoxia-inducible factor 1α (HIF-1α) gene by RNA interference comprising a sense region and an antisense region, wherein the sense region comprises the sequence set forth in SEQ ID NO: 7 and the antisense region comprises a 100% reverse complement of SEQ ID NO: 7. The claims are further

directed to structural requirements of the siRNA, linkers, modifications, terminal caps, vectors, and cells comprising the vectors.

Reich et al. teaches siRNA molecules that target HIF-1α mRNA and inhibit the expression of the HIF-1α gene via RNA interference. Reich et al. teach siRNA molecules and pharmaceutical compositions thereof which target HIF-1α. Reich et al. teach that the siRNA molecules have a first strand that is the same nucleotide sequence as a portion of the HIF-1α mRNA sequence and have a second strand of the siRNA duplex that is complementary to both the first strand of the RNA duplex and the same portion of the HIF-1α mRNA. The siRNA duplexes are about 17 nucleotides to 29 nucleotides in length, more preferably about 19 to about 25 nucleotides in length. Reich et al. teach suitable human HIF-1α target sequences.

Reich et al. teach that the siRNA can comprise two separate strands or can comprise a single molecule in which two complementary portions are base-paired and are covalently linked by a single-stranded hairpin area, meeting the instant limitation of a nucleotide linker.

Reich et al. teach that the siRNA can contain modifications of one or more ribonucleotide bases and can contain one or more deoxyribonucleotide bases. Reich et al. teach that the siRNA can be altered by the addition of non-nucleotide material, such as to the ends of the siRNA or to one or more internal nucleotides of the siRNA, meeting the instant limitation of a terminal cap. Reich et al. teach that the siRNA can be modified with modifications that make the siRNA resistant to nuclease digestion.

Reich et al. teach that the siRNA can also comprise a 3'-overhang on one or both strands and that is 1 to 6 , more preferably 1 to 5, more preferably 1 to about 4, more preferably about 2 to about 4 nucleotides in length. The overhangs can be modified with dithymidylic acid (TT) or diuridylic acid (UU). Reich et al. teach that in order to enhance stability of the siRNA, the 3' overhangs can be stabilized against degradation by substitution by modified analogues.

Reich et al. teach that the siRNA can be expressed from plasmids using any suitable promoter either as two separate, complementary RNA molecules or as a single RNA molecule with two complementary regions. Reich et al. teach that the siRNA can be expressed from recombinant viral vectors and delivered to human cells. The siRNA molecules can be expressed from a recombinant viral vector either as two separate complementary nucleic acid molecules or as a single nucleic acid molecule with two complementary regions. The viral vector can be derived from adenovirus.

Reich et al. teach compositions comprising the siRNA molecules and pharmaceutically acceptable carriers.

Reich et al. teach a siRNA molecule wherein the sense strand has the following sequence: AAGATGACATGAAAGCACAGA (see column 17, SEQ ID NO: 44). The sequence of Reich et al. is 21 nt in length and comprises the instant sequence except for the last nucleotide (t). Therefore, addition of a single nucleotide to the siRNA molecule of Reich et al. would directly anticipate claim 36.

Although Reich et al. teaches utilizing nucleotide linker hairpin regions, Reich et al. do not teach non-nucleotide linkers. Although Reich et al. teaches modifying siRNA

molecules to enhance resistance to nuclease digestion, Reich et al. do not specifically teach phosphorothioate nucleotides, universal bases ribonucleotides, or acyclic nucleotides.

Fosnaugh et al. teach siRNA molecules assembled from two separate fragments, wherein one fragment comprises the sense region and the other fragment comprises the antisense region. The fragments can be covalently connected via a linker molecule, wherein the linker molecule can be a polynucleotide linker or a non-nucleotide linker. The siRNA molecules can comprise modified purines or pyrimidines. Fosnaugh et al. teach phosphorothioates at the 3' end of the antisense region, one to five phosphorothioates at the 5' end of the antisense region, and modifications to the 3' terminal overhangs including universal bases or acyclic nucleotides. Fosnaugh et al. teach that chemical modifications of siRNA constructs dramatically increase serum stability, improve the stability of the interaction with target RNA sequences, and improve nuclease resistance.

Given that Reich et al. teaches a siRNA molecule targeting HIF-1α, wherein each strand is 21 nucleotides in length that comprises the instant sequence except fort the last nucleotide and teaches that siRNA molecules of the invention are 19 to 25 nucleotides in length, it would have been obvious and well within the technical grasp of the skilled artisan to add one nucleotide to the sequence of Reich et al. and arrive at a siRNA within the instant genus. The siRNA molecule of Reich et al. is targeted to the same region as the instant siRNA and adding one nucleotide is within the size range of Reich et al. Extending the siRNA sequence of Reich et al. within the size range of

Reich et al. is within the realm of routine optimization/design choice.

It would have been obvious to one of ordinary skill in the art to incorporate the specific structural configurations and chemical modifications of the siRNAs of Fosnaugh et al. into the siRNA molecules specific for HIF-1α of Reich et al.

One would have been motivated to incorporate the specific structural configurations and chemical modifications of the siRNAs of Fosnaugh et al. into the siRNA molecules specific for HIF-1α of Reich et al. because Reich et al. teaches the concept of incorporating chemical modifications to increase siRNA resistance to nuclease digestion and incorporating a hairpin configuration. Since Reich et al. teach these elements, one would have certainly been motivated to incorporate other linkers or chemical modifications that were known to add the same benefits to siRNA molecules, as taught by Fosnaugh et al. Fosnaugh et al. teach that chemical modifications of siRNA constructs dramatically increase serum stability, improve the stability of the interaction with target RNA sequences, and improve nuclease resistance.

It would have been prima facie obvious to perform routine optimization to determine the optimal structural configuration (i.e. presence of linkers) and optimal chemical modifications of the siRNA molecules, as noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the particular chemical modifications or linkers used was other than routine, that the

products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

One would have a reasonable expectation of success given that each of the modifications and linkers were known in the art at the time the invention was made to add benefits to siRNA molecules, as evidenced by both Reich et al. and Fosnaugh et al. One would reasonably expect for the modifications and structural elements of the siRNA molecules of Fosnaugh et al. to yield the same benefits to the siRNA molecules targeted to HIF-1α of Reich et al.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Declaration of Chuan Li, PH.D.

Applicant argues that Li provides evidence that a siRNA comprising SEQ ID NO: 7 has unexpectingly superior activity as compared to other siRNA molecules.

However, the three siRNA molecules that are compared to the siRNA molecule comprising instant SEQ ID NO: 7 are directed to different regions of the target sequence, wherein the siRNA of Reich et al. resulting from extension by one nucleotide, which is within the size range taught by Reich et al., would in fact comprise instant SEQ ID NO: 7 and be within the instant genus of molecules as claimed. Therefore, the data is not unexpected in comparison with the siRNA molecule of Reich et al.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 36, 38-42, 45-59, 62, and 63 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 36 has been amended to require for the sense region to be between 19 and 30 base pairs in length with no length limitation for the antisense region. It is noted

that the sense region would not be 19 to 30 "base pairs" in length, but rather 19 to 30 bases in length given that the sense region is within one strand. Appropriate correction/explanation is required.

Furthermore, the instant specification does not disclose or contemplate siRNA molecules wherein the sense region is 19 to 30 nucleotides in length and the antisense region has no length limit, thereby embracing those with much longer antisense regions.

MPEP §2163.06 notes:

> If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).

MPEP §2163.02 teaches that:

> Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application.

A review of the specification does not reveal support for where the claim amendments are found. Should applicant disagree, applicants are encouraged to point out with particularity by page and line number where such support might exist for each claim limitation added in the amended claims filed on 6/18/09.

There is no support for this claim limitation in the claimed priority documents. Therefore, the effective filing date of the instant claims is considered, for purposes of prior art, to be 11/2/06, which is the filing date of the instant application.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AMY BOWMAN whose telephone number is (571)272-0755. The examiner can normally be reached on Monday-Thursday 6:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AMY BOWMAN
Examiner
Art Unit 1635

/AMY BOWMAN/
Primary Examiner, Art Unit 1635